Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 58, No. 16, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.06.047

EDITORIAL COMMENT

How Much Statin Intervention Is Enough?*

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Numerous large clinical trials have now demonstrated that lowering low-density lipoprotein (LDL) levels with statins is highly beneficial (1). The intervention results in a significantly lower risk of both fatal and nonfatal coronary and cerebrovascular events in middle-aged men of European descent, who comprise the majority of patients studied. Available evidence expanding those findings to other population groups (women of all ages, younger and older men, and men and women of non-European lineage) is variable, often highly suggestive, but not indisputably definitive.

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Clinical trials directed at answering the question "how low an LDL is low enough?" have not clearly identified an LDL level below which there is no further lowering of vascular risk. Recent trials, however, have suggested that if such an LDL level exists, it is much lower than might have been earlier expected (2,3).

The paper by Lee et al. (4) in this issue of the *Journal* is an indirect attempt to explore this issue further. It has several shortcomings.

1. It is not a randomized trial but rather an observational comparison of patients after a myocardial infarction (MI) with LDL levels at the time of presentation lower than 70 mg/dl and who subsequently were, or were not, treated with statins.
2. Beyond the index lipid levels, no further LDL (or other) levels are reported.
3. The index LDL level was drawn within 24 h of the onset of MI symptoms to avoid the confounding effect of an acute MI dramatically, but temporarily, lowering LDL levels. Even though the index LDL was obtained with 24 h of the MI, the reported index LDL levels may not be representative of the patient's free-living levels.

These are indeed serious shortcomings. The report is nevertheless provocative.

This report joins others (5) suggesting that statin therapy may have significant benefits on vascular events in the immediate post-MI period and in the first year of follow-up, even in those whose LDL levels are already quite low (6). These reports cannot indicate if that effect is mediated through LDL lowering, a "pleiotropic" effect, or both.

These findings raise the possibility that a clinical trial of statin therapy with a placebo arm might still be ethically acceptable, although careful monitoring of LDL levels (with statin intervention if LDL levels rose above current LDL targets) would be required.

Such a trial could also address the lingering concern that very low LDL levels might themselves be a risk for the development of some other serious, nonvascular disorders (7). Currently, the impressive success of statins in vascular disease trials has made it much more difficult to study any potential drawbacks to aggressive LDL lowering.

Finally, such a trial might address the interesting question of whether achievement of very low LDL levels would obviate the need to aggressively modify other risk factors. If, as Roberts (8) suggested some time ago, LDL is the necessary substrate for atherogenesis, without which atherosclerosis does not progress, then achievement of extremely low LDL levels might be worthwhile, particularly if it can be done without significant risk. In this regard, it is interesting that in both the TNT (Treating to New Targets) and JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) studies (2,3), high-density lipoprotein levels ceased to be predictors of vascular risk in those with very low LDL levels.

In short, whether the benefits of statin therapy persist even at very low LDL levels can only be answered in a placebo-controlled clinical trial. Based on these and other similar findings, it is a trial worth considering.

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Key Words: low-density lipoprotein cholesterol ■ myocardial infarction ■ statin.